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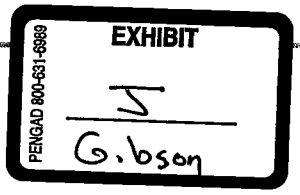

Mechanisms, Manifestations, and Management of Digoxin Toxicity in the Modern Era

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Abstract

Because of the common use of digoxin and because of its narrow therapeutic index, digoxin toxicity has been prevalent historically and, therefore, most clinicians are well aware of the classical dose/concentration-related signs and symptoms of toxicity. Yet, in the modern era the incidence of digoxin toxicity has been declining for a variety of reasons, including a new (lower) therapeutic range, the development of more effective drug therapies for heart failure, and more accurate dosing methods. In addition, digoxin toxicity, once commonly fatal, can now be quickly and effectively treated by the emergency administration of antidigoxin Fab fragments. Indeed, it may be possible to expand the use of Fab fragments to select patients with non life-threatening digoxin toxicity, in order to save costs and improve patient comfort. Most cases of digoxin toxicity are caused by inappropriately high dosages, which are usually prescribed in the setting of renal dysfunction, while other cases can be attributed to system errors such as multiple prescriptions, poor patient counseling, or errors in transcribing. With modern computerized prescribing systems, such as direct physician order entry and prompts that alert the clinician to the potential for error, it is possible to decrease the incidence of digoxin toxicity even further. A realistic goal is to nearly eradicate once commonplace digoxin toxicity or at least make its occurrence a rare event.

Throughout its more than 230 years of clinical use, the picture of digoxin toxicity has continued to evolve.

Early in its clinical use, it was relatively common to employ a strategy of escalating the dose of digoxin until adverse effects were observed. Indeed, this antiquated practice resulted in a clear clinical description of the various manifestations of digoxin toxicity, which are now well known to most clinicians.

Subsequent important clinical advances, however, led to a decline in the frequency of digoxin toxicity. Firstly, routine clinical serum digoxin concentrations became available, with the resulting acceptance of a therapeutic range.[1-3] Secondly, pharmacokinetic methods were utilized to develop dosing guidelines designed to achieve digoxin concentrations within the therapeutic window.[4,5] Simultaneously, for those unfortunate patients who experienced life-threatening digoxin toxicity, the creation, approval, and subsequent commercial availability of the Fab portion of digoxin antibodies proved to be much more effective than other treatments. Simply put, lives have been saved because of the administration of anti-digoxin Fab fragments. Most recently, the results of the DIG (Digitalis Investigative Group) trial,[6] published

in 1997, were crucial in clarifying the place of digoxin in the treatment of heart failure relative to other therapies such as β-adrenoceptor antagonists and angiotensin II type 1 antagonists. *Post-hoc* analyses of the DIG trial have helped further refine the clinical use of digoxin, including its therapeutic range.[7,8]

Thus, the evolution of knowledge regarding the clinical use of digoxin has resulted in a declining frequency and a different pattern and profile of digoxin toxicity. Nevertheless, patients still experience concentration-related digoxin toxicity as a result of dosing errors. The purpose of this article, therefore, is to review the clinical problem of digoxin toxicity in the modern era.

1. Pharmacology

An understanding of the complex pharmacological actions of digoxin will help to explain its toxic manifestations.[9-12]

Digoxin is a weak positive inotrope that indirectly increases calcium availability to the contractile elements of the myofibril by inhibiting Na^+-K^+ ATPase.[13,14] Inhibition of this ATPase results in an increase in intracellular Na^+ which, in turn, causes the Na^+-Ca^{2+} exchanger to increase intracellular Ca^{2+}. At high/toxic digoxin concentrations, the storage capacity of the sarcoplasmic reticulum for Ca^{2+} becomes saturated, causing spontaneous release and reuptake of Ca^{2+}. Ca^{2+} overload coupled with the Na^+-Ca^{2+} exchanger, cause the inward movement of Ca^{2+} and Na^+ during diastole that results in small electrical depolarizations termed afterdepolarizations.[15,16] These oscillations can summate, reach threshold, and cause rapid repetitive electrical impulses and/or trigger re-entry. The afterdepolarizations triggered indirectly by excess Ca^{2+} (i.e. they are an extension of the positive inotropic action of digoxin) more than likely underlie the primary mechanism for most digoxin-induced tachycardias.[17,18]

The effects of digoxin on the autonomic nervous system have also been well described.[9-11] Digoxin has parasympathomimetic actions that clinically manifest by increasing vagal tone to the sinus and atrioventricular (AV) nodes, thus decreasing HR and slowing conduction through the AV node. In patients with heart failure, digoxin has anti-sympathetic effects, including restoration of baroreceptor sensitivity (which is decreased in low-output heart failure).[19-21] The exact underlying mechanism for these effects remains unclear but the sympatholytic actions first appear at relatively low digoxin concentrations – below those needed to cause a measurable increase in the force of contraction. In heart failure, low concentrations of digoxin decrease serum norepinephrine (and other neurohormonal) levels.[22] Indeed, many authors now feel that the therapeutic effects of digoxin (such as those noted in the DIG trial) in patients with heart failure can be predominantly attributed to its action as a sympatholytic, blocking compensatory neurohormones (not unlike β-adrenoceptor antagonists) rather than its well known inotropic effects.[14,21,22]

Digoxin is a substrate for p-glycoprotein, a membrane transport pump that is present not only in the intestine but also in many other organs such the CNS and the kidney. P-glycoprotein modulates the oral absorption of digoxin, in addition to its renal excretion and movement across the blood-brain barrier.[23] The oral bioavailability of digoxin ranges from 70% to 90%.[24] The mechanism for well described drug interactions with digoxin can, in many cases (e.g. verapamil, quinidine, and amiodarone), be attributed to the inhibition of p-glycoprotein.[25,26] By inhibiting p-glycoprotein, these agents increase serum digoxin concentrations by increasing its intestinal absorption and decreasing renal clearance.

The elimination half-life ($t^1/_2$) of digoxin in patients with normal renal function is about 1.6 days but can be 4–6 days in patients with end-stage renal dysfunction and, therefore, without appropriate intervention, toxic effects can persist for several days to weeks.[24] Digoxin has a relatively large volume of distribution (5–7 L/kg) and is highly tissue bound, making dialysis ineffective in the treatment of toxicity.[24]

The accepted therapeutic range for digoxin has changed in the past few years. Historically, the window was 1.0–2.5 nmol/L (0.8–2.0 μg/L), with toxicity more common above concentrations of 2.5 nmol/L.[1,2] While the upper border of this range still has useful value in aiding the diagnosis of digoxin toxicity, concentrations between 0.6 and 1.2 nmol/L (0.5–1.0 μg/L) [i.e. about half of the concentrations felt to be desirable in the past] should now be targeted in patients with heart failure. The data supporting this new range come from *post-hoc* analyses of major multicenter clinical trials. Initially, Adams et al.[7] analyzed data from two large digoxin 'withdrawal' studies. In general, patients with low serum concentration of digoxin (0.6–1.1 nmol/L [0.5–0.9 μg/L]) fared better, including having statistically fewer episodes of heart failure exacerbation, compared with those receiving placebo. Consistent with these data was the *post-hoc* analysis of the DIG trial (figure 1).[8] In that analysis, low digoxin concentrations (0.6–1.0 nmol/L or 0.5–0.8 μg/L) were associated with better clinical outcomes and lower mortality. In contrast, digoxin concentrations >1.5 nmol/L (1.2 μg/L) were associated with higher mortality rates and a greater incidence of digoxin toxicity. Although the authors attempted to control the confounding factors that may have influenced mortality and digoxin levels (e.g. concurrent renal dysfunction), cause and effect were difficult to definitively ascertain. Nonetheless, these findings have fueled a clinical trend to use lower dosages of digoxin (0.125 mg/day vs 0.25 mg/day) in most patients with heart failure; this should result in lower rates of digoxin toxicity.

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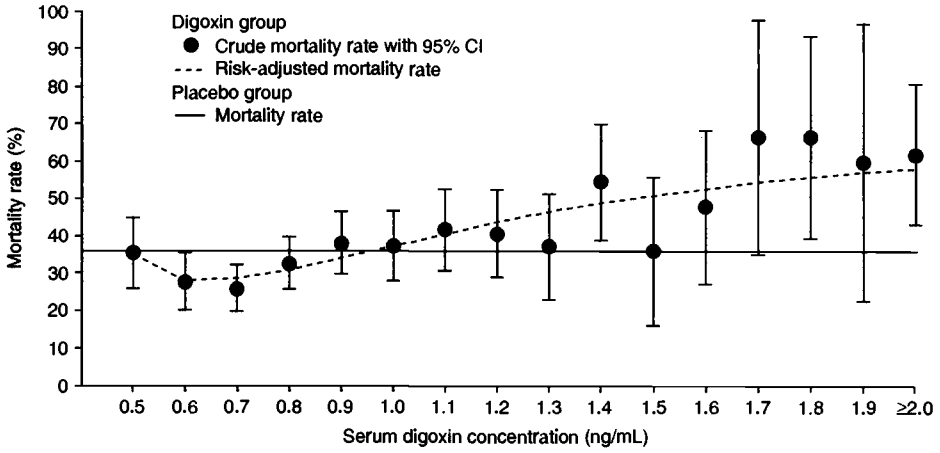

Fig. 1. Relationship between serum digoxin concentration and all-cause mortality in a *post-hoc* analysis of the DIG (Digitalis Investigative Group) trial (reproduced from Rathore et al.,[8] with permission). Note the statistically significant decrease in mortality (compared with placebo) at digoxin concentrations of 0.6–0.7 ng/mL (μg/L) and the trend toward increasing mortality at concentrations >1.0 ng/mL. These data have helped to redefine the therapeutic range of digoxin to a lower window of concentrations and may be expected to contribute to a further decline in the incidence of toxicity.

2. Incidence and Causes

It is useful to compare previous estimates of digoxin toxicity with more recent data. For instance, in a classic paper in 1971 by Beller et al.,[2] nearly 25% of all patients treated with digoxin were classified as having "definite toxicity" and an additional 6% were felt to have signs or symptoms of "possible" digoxin toxicity. Importantly, >40% of the patients with definite digoxin toxicity died. Data from the 1980s and the 1990s put the incidence of digoxin toxicity at about 4–5% in patients receiving digoxin.[27-29] In the DIG trial,[6] digoxin toxicity was diagnosed in 11.9% of patients receiving digoxin and in 7.9% of those receiving placebo; underscoring the sometimes difficult job of diagnosing digoxin toxicity. If one presumes that the incidence of falsely diagnosed digoxin toxicity was 7.9% (the incidence of digoxin toxicity in the placebo group), then the actual incidence of digoxin toxicity in the DIG trial was again about 4%.[6,30] In 1996, we analyzed the database of a large consortium of academic medical centers in the US and found that digoxin toxicity occurred in <0.1% of all hospital admissions (836 cases in 1 189 839 admissions).[31] This demonstrates a relatively impressive decline over several decades in the magnitude of digoxin toxicity as a medical problem and correlates well with the now widespread use of serum concentration monitoring, improved dose-determination methods and awareness of drug interactions.

Why do patients still experience toxicity from digoxin? Aside from purposeful overdoses or suicide gestures, one can assume that digoxin toxicity occurs because of some medical error made by either the clinician or the patient and, thus, that most of these cases are preventable. Clearly one of the most important risks is the presence of renal dysfunction: in one series,[32] two-thirds of patients with digoxin toxicity had moderate-to-severe renal disease (creatinine clearance <50 mL/min for women or <60 mL/min for men). We analyzed a series of 17 patients (16 with definite digoxin toxicity), in part, to gain an insight to this question.[31] Of the 16 patients, six (37.5%) experienced toxicity due to worsening renal function without a subsequent decrease in the dose of digoxin, another four patients (25%) experienced toxicity because the initial dose was too high for the patient (according to their renal function), and in one patient the dose was not decreased when amiodarone was added. Therefore, most patients experienced digoxin toxicity simply because they received a dosage that was too high (i.e. their dosage was not appropriately individualized). Four more patients (25%) experienced toxicity because, although they were prescribed an appropriate dosage, they self-administered digoxin inappropriately. For example, two patients received prescriptions for both 0.25 and 0.125 mg/day and the other two patients mistakenly took 0.25mg every day instead of every other day. Simple patient counseling and proper follow up could have prevented all four of these episodes of digoxin toxicity. The last patient received an appropriate dosage but the ultimate cause of digoxin toxicity could not be determined. Hence, nearly all of the cases reviewed (in this albeit small series) could have been prevented; some were clinician errors in judgment (e.g. wrong dosage) and some were 'system' errors (e.g. multiple prescriptions or lack of proper counseling). Regardless, it may be possible to put into place safeguards such as pharmacy computer systems with prompts and precautions that could decrease the incidence of digoxin toxicity even further (see section 5).

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3. Manifestations

The signs, symptoms, and manifestations of digoxin toxicity have been well documented over the years.[9-12,16] They are traditionally divided into extra-cardiac and cardiac manifestations and although nearly every form of toxicity has been attributed to digoxin, a number are highly associated with true toxicity. Although unusual, digoxin toxicity has been reported to result in curious visual disturbances such as flashing lights, halos, and color disturbances (green-yellow patterns). More commonly, patients simply complain of hazy or blurred vision. Likewise, hallucinations have been reported but more common is the non-specific complaint of acute fatigue. Anorexia and nausea are extremely common; vomiting is less likely but not uncommon. These gastrointestinal symptoms occur in 30–70% of patients with reported digoxin toxicity.[6,28,29] Lacking the relatively unusual adverse effects that are somewhat pathognomomic for digoxin toxicity, often symptoms are nonspecific (e.g. nausea, blurred vision, and/or fatigue) and, therefore, the diagnosis of digoxin toxicity based solely on extra-cardiac symptoms can be difficult. Indeed in several recent large series of digoxin toxicity,[28,29,33] nausea/vomiting, anorexia, and fatigue are consistently the most frequently observed extra-cardiac symptoms.

One sign of serious digoxin toxicity that clinicians should always specifically target is hyperkalemia (i.e. serum potassium concentration >5.0 mEq/L [>5.0 mmol/L]). Hyperkalemia results from digoxin blocking Na^+-K^+ ATPase diffusely throughout the body and the resultant leak of potassium from its intracellular home into extracellular spaces. Measurable hyperkalemia generally indicates extremely high concentrations of digoxin, often in the setting of renal dysfunction and traditionally prompts emergency treatment measures.

Digoxin has also been reported to cause nearly every rhythm disturbance; several are nearly diagnostic of digoxin toxicity and a number are rarely, if ever, due to digoxin.[12,16,34] Those that should be considered as digoxin-toxic rhythms unless proven otherwise (of course, in patients receiving digoxin) are new-onset Mobitz type I AV block (Wenckebach periodicity), accelerated junctional rhythm with or without high-degree AV block, non-paroxysmal atrial tachycardia with AV block, and bidirectional ventricular tachycardia. In patients with established atrial fibrillation, the regularization of ventricular rhythm represents complete heart block with an accelerated junctional escape due to digoxin toxicity. But analogous to the extra-cardiac signs and symptoms of digoxin toxicity, in many cases digoxin-induced arrhythmias are often nonspecific and may not necessarily alert the clinician to the toxic state. These include sinus bradycardia, premature ventricular complexes (PVCs) [e.g. bigeminy], and nonsustained ventricular tachycardia. To gain an appreciation of the relative frequency of these rhythm disturbances, one could analyze multicenter studies that use digoxin antibody Fab fragments.[32,35] In the final report of one prospective trial,[35] it was reported that patients had experienced third-degree heart block (53%), sustained ventricular tachycardia (46%), ventricular fibrillation (33%), and asystole (11%). However, one criterion for entry into this trial was that patients had life-threatening arrhythmias. In other reports that included patients with non life-threatening digoxin toxicity, less serious rhythm disturbances (e.g. Mobitz type I second degree AV block, junctional rhythm, sinus bradycardia, or PVCs) were most common.[28,33] PVCs and digoxin-related tachycardias have historically been noted to be exacerbated by electrolyte disorders such as hypokalemia, hypomagnesemia, and hypercalcemia. Clinicians should also be aware of rhythm disturbances that are usually not attributable to digoxin toxicity. These include any supraventricular tachycardia with a rapid ventricular response and Mobitz type II AV block (the site of the block is usually below the AV node, unlike Mobitz type I block which is usually within the AV node).

Some authors have attempted to differentiate the signs and symptoms of toxicity based upon acute (e.g. purposeful or inadvertent overdose) or long-term (i.e. those with heart failure who are prescribed a maintenance dosage of digoxin that is too high) use.[36,37] However, these differences may simply be because of the magnitude of digoxin exposure. That is, patients who have ingested a large quantity of digoxin in a suicide attempt are more likely to display hyperkalemia and serious ventricular arrhythmias than those who have been prescribed a maintenance dosage that is too high (e.g. 0.25 mg/day instead of 0.125 mg/day). Regardless, as one can appreciate, it is sometimes difficult to diagnose digoxin toxicity because many of the more common signs or symptoms are relatively nonspecific (e.g. anorexia, PVCs) and could be due to other disorders. It is here that the determination of digoxin concentration is very useful. Although there is some overlap in 'therapeutic' and toxic levels, toxic symptoms are clearly more common above 2.5 nmol/L (2.0 μg/L) [figure 2].

4. Treatment of Digoxin Toxicity

Since the serious manifestations of digoxin toxicity are new-onset rhythm disturbances, traditional therapy has focused on these disorders. In patients with high-degree symptomatic AV block, intravenous atropine and temporary pacing have been recommended.[9-12] In patients with symptomatic ventricular arrhythmias, intravenous lidocaine and phenytoin have been recommended as the treatments of choice.[9-12] However, we can see little reason to recommend these therapies any longer because of the creation and commercial availability of digoxin antibody Fab

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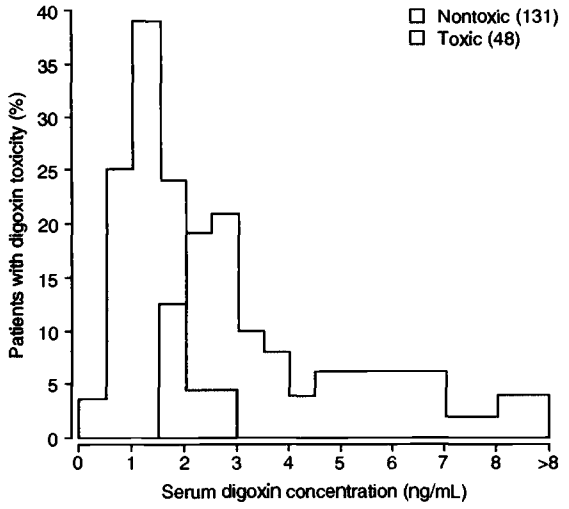

Fig. 2. Relationship between serum digoxin concentration and the diagnosis of digoxin toxicity in 179 patients from Dr Thomas Smith's original analysis in 1970 (reproduced from Smith et al.,[1] with permission). Although there is some overlap between toxic and non-toxic concentrations, the value of determining a digoxin level to aid in the diagnosis of digoxin appears clear: 87% of the patients with digoxin toxicity have concentrations >2.0 ng/mL (μg/L).

fragments. Concurrent therapies with agents such as activated charcoal, colestyramine, or colestipol have also been recommended in an attempt to bind digoxin in the gut.[38-40] These facilitate gastrointestinal elimination but also increase the systemic clearance of digoxin. Through both passive diffusion and perhaps enterohepatic recycling of digoxin, the intestine acts as a sink or dialysis membrane, with the binding resin or charcoal aiding in the elimination of digoxin. It appears as if activated charcoal is superior to binding resins such as colestyramine in patients who are likely to have significant quantities of digoxin present in the intestine, such as after a purposeful overdose.[41] However, it remains unclear which type of therapy (resins vs charcoal) is preferred in patients experiencing digoxin toxicity in the post-absorptive state. These therapies may play a role, predominantly in patients with non life-threatening signs or symptoms and concurrent renal dysfunction, where digoxin elimination would ordinarily take very long periods of time.

The use of Fab portions of antidigoxin antibodies prepared from sheep antiserum to reverse digoxin toxicity in humans was first reported in 1976.[42] In comparison to complete IgG antidigoxin antibodies, the use of just the Fab portion (cleaved from the Fc portion by papain) has the advantages of: (i) lower immunogenicity and incidence of allergic reactions; (ii) increased distribution to extravascular tissue sites; and (iii) increased systemic clearance by glomerular filtration and renal elimination.[43] Digoxin has a higher affinity for binding to the antidigoxin Fab fragment than to its physiologic receptor responsible for toxic signs and symptoms. Therefore, the Fab fragments rapidly bind digoxin in the blood and interstitial fluid, causing a redistribution from intracellular tissue stores to the central compartment. Thus, despite the large volume of distribution of digoxin, the onset of action of antidigoxin Fab fragments in reversing digoxin toxicity is rapid (minutes). The volume of distribution of antidigoxin Fab is 0.4 L/kg and $t^1/_2$ is about 12–20 hours in patients with normal renal function ($t^1/_2$ is increased 10-fold in patients with severe renal dysfunction).[43] Although generally well tolerated, there are a number of adverse effects and complications of therapy to consider.[16,32,43] Minor allergic reactions may occur, although, to our knowledge, anaphylaxis has not been reported. Since digoxin will be immediately neutralized (and the activity of Na^+-K^+ ATPase restored), exacerbation of heart failure (in left ventricular dysfunction), accelerated ventricular response (in atrial fibrillation), and hypokalemia may be observed. In the final report of a multicenter trial of patients with life-threatening digoxin toxicity, the rapid development of hypokalemia was documented in 4% of patients after the administration of antidigoxin Fab fragments.[35] Recrudescent digoxin toxicity after an initial response to antidigoxin Fab has been reported in about 3% of patients in large multicenter trials.[32] Although there is no clear evidence that the stability of the Fab-digoxin complex wanes with time (releasing free digoxin), it is possible that the administration of inadequate amounts of Fab could result in a rebound increase in free digoxin concentrations caused by shifts in tissue stores. In a large post-marketing surveillance study,[32] it was discovered that the risk of recrudescent digoxin toxicity was six times more likely if patients were given less than half of the calculated full neutralizing dose. It should also be noted that, from a practical viewpoint, serum digoxin concentrations cannot be usefully monitored after the administration of Fab fragments. Digoxin concentrations rise rapidly (as much as 30-fold) as the Fab fragment pulls digoxin from extravascular tissue stores into the plasma but these concentrations reflect the levels of the Fab-digoxin complex, not free unbound digoxin (which is negligible).

The administration of antidigoxin Fab to patients with digoxin toxicity is remarkably effective. In large multicenter trials, antidigoxin Fab has been shown to be 80–90% effective in rapidly and completely reversing all signs and symptoms of digoxin toxicity.[32,35] In most patients, the complete reversal of toxicity occurred within 4 hours.[35] The major reasons for lack of effectiveness were inadequate dosing and incorrect diagnosis. It is our opinion that antidigoxin Fab was used aggressively and perhaps sometimes inappropriately when it first became commercially available in 1986. However, antidigoxin Fab is expensive and these two issues (initial over-zealous use and high cost) have led to its subsequent, more limited, utilization in only those patients with

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life-threatening arrhythmias or hyperkalemia. For instance, in more recent series of digoxin toxicity (including life-threatening and non-life-threatening presentations), antidigoxin Fab was only used in 4–6% of patients with this diagnosis.[29,31]

While it is clear that antidigoxin Fab should be administered to anyone with severe symptoms of digoxin toxicity, we think its use should be liberalized to include some patients with non life-threatening toxicity. In a burden-of-illness analysis, we found that hospitalization (bed) costs accounted for 93% of the total costs of digoxin toxicity.[31] In those patients with non life-threatening toxicity, the usual clinical scenario is that the patient is admitted for close observation only (without an intervention specifically targeted for digoxin toxicity) and is discharged after the signs and symptoms have resolved and the digoxin level has dropped below 2 μg/L. Indeed, the cost of digoxin toxicity correlated linearly with the digoxin concentration at the time of admission (figure 3). As a result of these data, we performed a cost-effectiveness analysis of antidigoxin Fab administration for use in patients with non life-threatening toxicity.[44] A nomogram was constructed that may aid clinicians in the decision whether to use or not use antidigoxin Fab for these patients (figure 4). In general, patients with higher digoxin serum concentrations (e.g. >3.6 nmol/L [3.0 μg/L]) and poorer renal function (e.g. creatinine clearance <50 mL/min) could receive antidigoxin Fab to reduce the length of stay and overall costs.

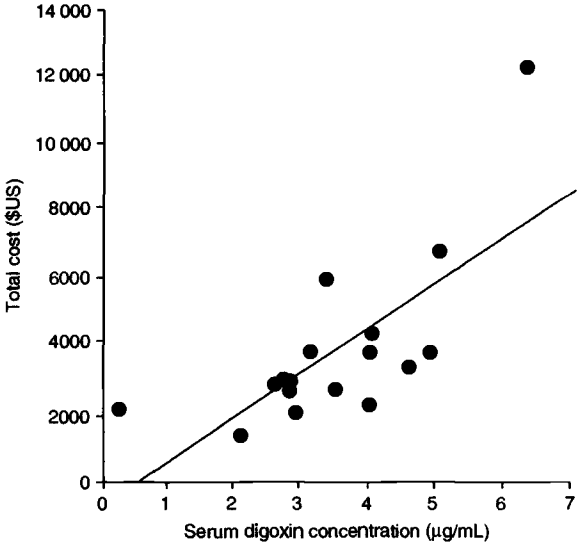

Fig. 3. Relationship between total cost (1995 values) of an episode of digoxin toxicity and digoxin concentration at admission in 17 patients[31] ($r = 0.73$; $p < 0.01$) [the one patient with a low digoxin concentration was diagnosed in error]. Patients are generally observed until the digoxin concentration drops below 2 μg/L and symptoms resolve.

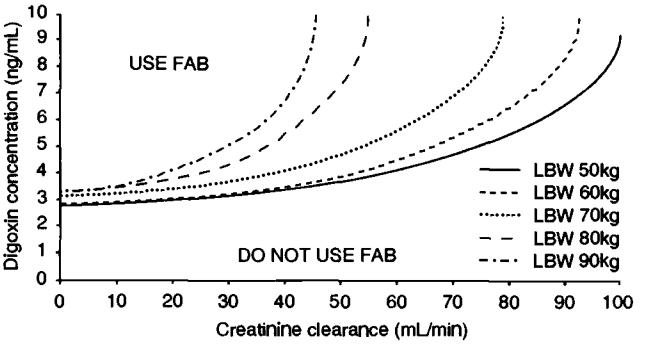

Fig. 4. Nomogram for the clinical use of antidigoxin Fab (FAB) in patients with non-life threatening digoxin toxicity based upon a pharmacoeconomic analysis. The decision to use FAB or not is based upon the digoxin concentration, renal function (creatinine clearance), and lean body weight (LBW). For intersects above each line for LBW, the use of FAB will reduce overall cost of care (and improve patient symptoms); the use of FAB is cost effective. For patients who fall below each line, the cost of care with use of FAB is increased and therefore, FAB should not be used for economic reasons (reproduced from DiDomenico et al.,[44] with permission).

There are two commercial preparations of antidigoxin Fab available in the US (DIGIBIND® and DigiFab™)[1] and both are dosed in the same manner. In the case of an acute ingestion (e.g. overdose) where the amount ingested is known, one may estimate the quantity of antidigoxin Fab by equation 1:

$$\text{Dose (no. of vials)} = \frac{\text{Total amount ingested (mg)}}{0.5^*}$$

* = mg of digoxin bound per vial of Fab

Alternatively, the estimation of the antidigoxin Fab dose can be completed by using a serum digoxin concentration in the following manner (equation 2):

$$\text{Dose (no. of vials)} = \frac{\text{Serum digoxin concentration (μg/L)} \times \text{weight (kg)}}{100}$$

To estimate the dose of anti-digoxin fab in milligrams (instead of vials), DIGIBIND® contains 38 mg/vial and DigiFab™ contains 40 mg/vial.

For the latter equation, the concentration used should be after the distribution from the central (blood) to the tissue compartment (i.e. at least 6 hours after the last dose). If the concentration is measured within this 6-hour window (during the distributive phase) the dose of antidigoxin Fab will be overestimated. If a distributive phase concentration is the only one available, using less than the full neutralizing dose (e.g. 50%) and observing for the resolution of symptoms has been suggested.[45] However, we recommend giving the full calculated dose if the patient has life-threatening symptoms: there is little harm (except excessive cost)

1 The use of trade names is for product identification purposes only and does not imply endorsement.

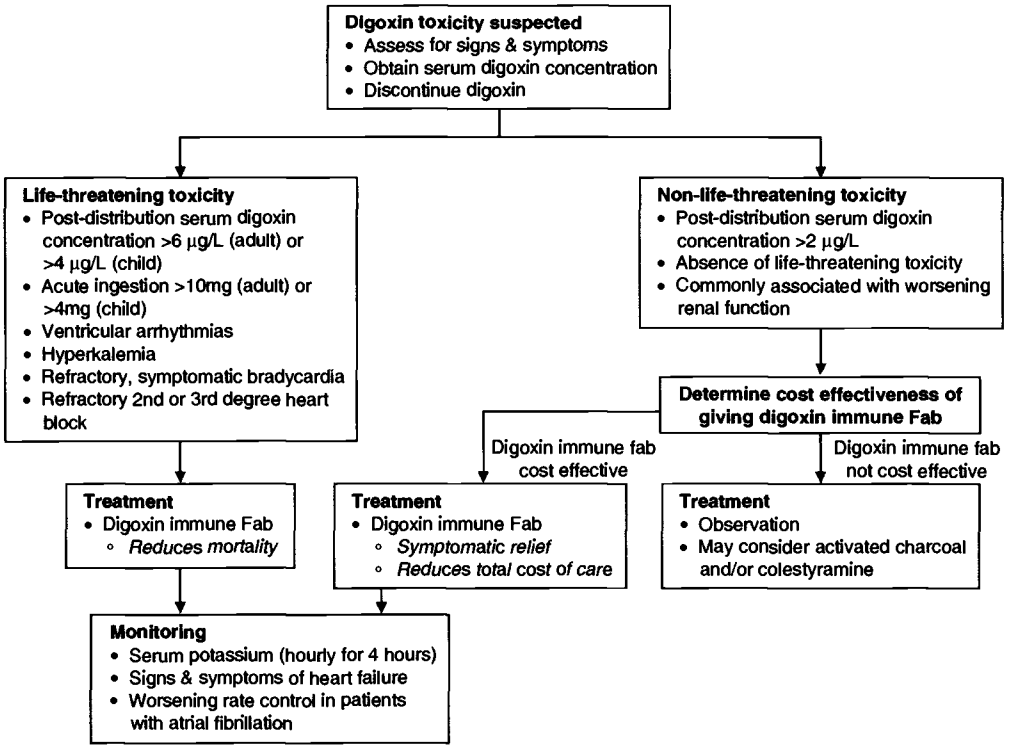

Fig. 5. Suggested algorithm for the clinical approach to digoxin toxicity.

of giving 'too much' Fab and this strategy minimizes the risk of recrudescent digoxin toxicity. Further, the strategy of giving less than the full estimated dose of Fab has not been systematically evaluated in large clinical trials.

In summary, the approach to digoxin toxicity can be summarized by grouping the patient's initial presentation into one of two categories (figure 5): (i) life-threatening toxicity (i.e. those with ventricular tachycardia, ventricular fibrillation, symptomatic high-degree AV block, sinus arrest, and/or hyperkalemia); and (ii) non life-threatening but symptomatic toxicity. In those patients with serious forms of toxicity, antidigoxin Fab fragments are administered for therapeutic reasons (to save a life and reverse serious symptoms), whereas in those with less serious presentations it may be administered on the basis of reducing the costs of care (by abbreviating hospital stay) and improving patient comfort. In patients with excess digoxin but with only very mild or no symptoms of digoxin toxicity, a conservative approach is recommended. One may consider binding resins or activated charcoal in order to enhance digoxin elimination (particularly in patients with renal dysfunction).

5. Prevention

Obviously, it is preferable to prevent digoxin toxicity rather that treat it. Adverse drug events, including digoxin toxicity, often result from errors in drug ordering, transcribing, dispensing, administering, or monitoring.[46] It has been estimated that 20–69% of all adverse drug events may be preventable.[47-50] Likewise, given that most episodes of digoxin toxicity result from the failure to adjust the dosage in the presence of renal insufficiency or notable drug interactions,[31] it appears that most cases of digoxin toxicity could be avoided. There are some simple dose-determining guidelines that clinicians can use to prevent possible digoxin toxicity. For instance, one should initiate only 50% (e.g. 0.125 mg/day instead of 0.25 mg/day) of the dosage as estimated by Jelliffe's method[5] since this equation/nomogram was originally designed to achieve a steady-state digoxin concentration of 1.4 µg/L. Further, when adding agents known to interact with digoxin, such as amiodarone, the maintenance dosage of digoxin should be empirically cut in half (e.g. from 0.125 mg/day to 0.125mg every other day).

As computer technology continues to be integrated into the practices of medicine and pharmacy, embracing these technological advances may provide opportunities to prevent digoxin toxicity. As an important example, computerized physician order entry (CPOE) is being adopted at many healthcare facilities. Many of these CPOE systems utilize automated clinical decision support (CDS) technology, such as drug-allergy and drug-drug interaction checking. Several studies have shown that the use of these basic technologies reduces the incidence of adverse drug events.[51-54] The use of more sophisticated CDS systems has also been shown

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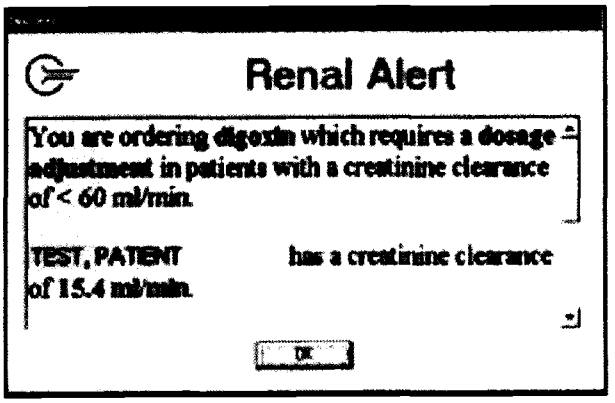

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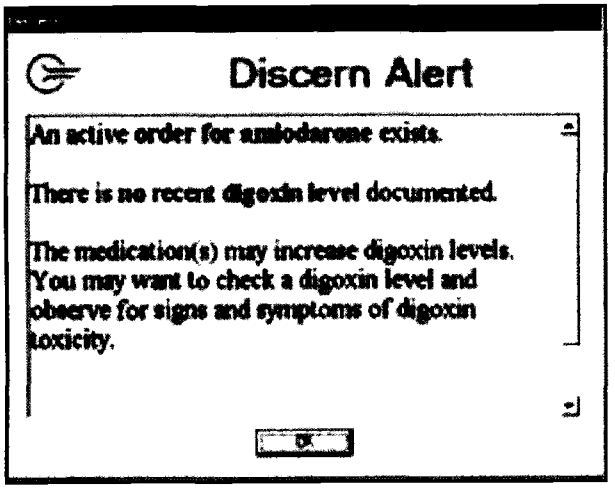

Fig. 6. Synchronous clinical decision support alerts for digoxin. Example of alerts that appear in real-time to digoxin-ordering clinician. Panel A alerts the ordering physician to the patient's renal insufficiency, suggesting dosage adjustment. Panel B alerts the clinician that the patient is also taking amiodarone, which may raise digoxin levels. Alerts also appear to the clinician ordering digoxin when electrolyte deficiencies are present that may increase the risk of digoxin toxicity (e.g. hypokalemia, hypomagnesemia).

to decrease adverse drug events related to anti-infective drugs[55] and to improve renal dosing of drugs.[56,57]

Because the risk of digoxin toxicity can be assessed using objective information readily available in a patient's chart, such as renal function, electrolyte levels, concomitant drug therapy, and serum digoxin concentration, it is an ideal target for the application of advanced CDS systems. We have developed such a system at the University of Illinois Medical Center.[58,59] The automated CDS rules for digoxin utilize patient-specific information recorded in the patient's electronic medical record, including serum electrolyte levels, estimated creatinine clearance, serum digoxin levels, and active orders for interacting drugs (e.g. amiodarone). When a clinician attempts to order digoxin (or an interacting drug in a patient already taking digoxin), the automated CDS system screens the patient's electronic medical record for scenarios associated with an increased risk of digoxin toxicity (renal insufficiency, drug-drug interaction, electrolyte deficiencies, or supra-therapeutic digoxin concentrations) and, if these conditions are present, warns the clinician in real-time, synchronous to the ordering process, suggesting measures to minimize digoxin toxicity (figure 6).

Similarly, for patients with active orders for digoxin, when new laboratory results are posted to the electronic medical record suggesting digoxin toxicity (i.e. elevated digoxin concentration) or the potential for digoxin toxicity (i.e. electrolyte deficiencies or worsening renal function), the CDS system alerts clinicians asynchronously by generating a printout at the patient's nursing station as well as an electronic communication (similar to an e-mail) to the patient's providers warning of the potential for digoxin toxicity. Utilizing this technology, potential cases of digoxin toxicity have been prevented[58] and inpatient prescribing of digoxin has improved.[60] While these computerized safeguards are currently only in place for patients who have been hospitalized, technology is being developed that could similarly prevent prescribing errors in ambulatory patients.

While technological advances such as automated CDS systems may reduce the incidence of digoxin toxicity, only a small minority of healthcare facilities utilize these advanced systems. In those healthcare settings without the benefit of advanced computer technology, education regarding the appropriate use of digoxin is critical in preventing medication errors that lead to digoxin toxicity. Given that renal insufficiency plays a significant role in the development of digoxin toxicity, educating clinicians on the importance of using the creatinine clearance as the preferred assessment of renal function (compared with serum creatinine) is important. We have found that clinicians sometimes assess renal function based on serum creatinine level alone rather than creatinine clearance. Consequently, they are more likely to overestimate renal function in women,[60] based on the 0.85 sex-based correction factor for women in the Cockcroft and Gault equation.[61] If clinicians rely solely on serum creatinine level to assess renal function, renal function in women may be overestimated, placing them at higher risk for digoxin toxicity.

6. Conclusion

Digoxin toxicity, once common, has declined for a variety of reasons including more accurate dosing methods and the routine availability of digoxin concentrations. Moreover, the results of large multicenter trials that have refined the role of digoxin, further characterization of drug interactions with digoxin, the

availability of more effective drugs for the treatment of heart failure, and the acceptance of a new (lower) therapeutic range can be expected to even further reduce the frequency of digoxin toxicity. Yet, digoxin toxicity still occurs and in the modern era most cases can and should be prevented. Many patients with digoxin toxicity are simply prescribed a dosage that is too high for their renal function or, alternatively, errors in prescribing or counseling occur. With modern technology, using tools such as CPOE and prompts that alert the clinician to the possibility of a prescribing error that could result in toxicity, it may be possible to all but eliminate digoxin toxicity making it a rare event in the future.

Digoxin toxicity was historically not only common but highly fatal. The commercial availability of digoxin immune Fab has provided a highly effective and life-saving treatment. It may be possible to expand the indications of these Fab fragments beyond life-threatening situations. In certain cases of non life-threatening toxicity, digoxin immune Fab can be cost effective, shortening hospital stay and reversing bothersome symptoms.

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